Dairy consumption, systolic blood pressure, and risk of hypertension: Mendelian randomization study

Mendelian Randomization of Dairy Consumption Working Group

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ABSTRACT

OBJECTIVE

To examine whether previous observed inverse associations of dairy intake with systolic blood pressure and risk of hypertension were causal.

DESIGN

Mendelian randomization study using the single nucleotide polymorphism rs4988235 related to lactase persistence as an instrumental variable.

SETTING

CHARGE (Cohorts for Heart and Aging Research in Genomic Epidemiology) Consortium.

PARTICIPANTS

Data from 22 studies with 171 213 participants, and an additional 10 published prospective studies with 26 119 participants included in the observational analysis.

MAIN OUTCOME MEASURES

The instrumental variable estimation was conducted using the ratio of coefficients approach. Using meta-analysis, an additional eight published randomized clinical trials on the association of dairy consumption with systolic blood pressure were summarized.

RESULTS

Compared with the CC genotype (CC is associated with complete lactase deficiency), the CT/TT genotype (TT is associated with lactose persistence, and CT is associated with certain lactase deficiency) of *LCT-13910* (lactase persistence gene) rs4988235 was associated with higher dairy consumption (0.23 (about 55 g/day), 95% confidence interval 0.17 to 0.29) serving/day; P<0.001) and was not associated with systolic blood pressure (0.31, 95% confidence interval −0.05 to 0.68 mm Hg; P=0.09) or risk of hypertension (odds ratio 1.01, 95% confidence interval 0.97 to 1.05; P=0.27). Using *LCT-13910* rs4988235 as the instrumental variable, genetically determined dairy consumption was not associated with systolic blood pressure (β=1.35, 95% confidence interval −0.28 to 2.97 mm Hg for each serving/day) or risk of hypertension (odds ratio 1.04, 0.88 to 1.24). Moreover, meta-analysis of the published clinical trials showed that higher dairy intake has no significant effect on change in systolic blood pressure for interventions over one month to 12 months (intervention compared with control groups: β=−0.21, 95% confidence interval −0.98 to 0.57 mm Hg). In observational analysis, each serving/day increase in dairy consumption was associated with −0.11 (95% confidence interval −0.20 to −0.02 mm Hg; P=0.02) lower systolic blood pressure but not risk of hypertension (odds ratio 0.98, 0.97 to 1.00; P=0.11).

CONCLUSION

The weak inverse association between dairy intake and systolic blood pressure in observational studies was not supported by a comprehensive instrumental variable analysis and systematic review of existing clinical trials.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Observational studies showed that dairy intake was associated with lower systolic blood pressure and lower risk of hypertension

WHAT THIS STUDY ADDS

Using a Mendelian randomization approach, we found that genetically determined dairy consumption was not associated with systolic blood pressure or risk of hypertension

Introduction

Raised blood pressure is an important risk factor for cardiovascular disease and has been the top single contributor to the global burden of morbidity and mortality, leading to 9.4 million deaths each year.[1] In clinical trials, lowering blood pressure has been shown to be effective in reducing the incidence of cardiovascular disease.[2] Each 5 mm Hg reduction in blood pressure is associated with a 20% lower risk of coronary heart disease and a 29% lower risk of stroke.[3]

Maintaining a healthy diet is critical for the prevention of hypertension[4]; whether dairy products should be incorporated into such a diet is, however, controversial. In epidemiological studies, the association of dairy consumption with blood pressure has been inconsistent. Several observational studies have reported inverse associations of dairy consumption with systolic blood pressure and risk of hypertension[5 6 7]; however, such associations were not observed in other studies.[8 9 10] Two meta-analyses of prospective cohort studies consistently indicated that dairy consumption was associated with lower systolic blood pressure and lower risk of hypertension.[11 12] Owing to the observational nature of the studies included, the reported associations might not indicate causality.

In recent years, Mendelian randomization analysis has been widely used to assess potential causal estimates of various risk factors with health outcomes. This approach has the advantage over traditional observational studies of minimizing confounding by using genetic markers as instrumental variables of environmental risk factors. An SNP (single nucleotide polymorphism) rs4988235 upstream from the lactase persistence gene (*LCT-13910*) has been consistently related to dairy intake in multiple populations,[13 14] representing a strong instrumental variable for analyzing the causal relation between dairy intake and disease risk.

In this study, using data collected from 32 studies with 197 332 participants, we performed an instrumental variable analysis to examine the possible causal effect of dairy consumption on systolic blood pressure and

Table 1 | Baseline characteristics of included cohorts

Study name	Ethnicity	Country	No of participants	Follow-up (years)	Men (%)	Age (years)	SBP (mm Hg)	Hypertension (%)	Antihypertensive drugs (%)	rs4988235 frequency (%)		
										CC	CT	TT
CGPS	White	Denmark	74 219	0	45	57	140	20	20	6	36	58
WGHS	White	USA	19 743	4	0	54	126	13	13	11	38	51
GESUS	White	Denmark	14 815	0	46	57	142	10	23	6	36	58
NHS	White	USA	11 287	26	0	53	NA	9	NA	14	41	45
ARIC (white)	White	USA	8233	6	47	54	118	29	19	9*	39*	52*
ARIC (African-American)	African	USA	1889	6	36	53	127	55	41	74*	25*	2*
HPFS	White	USA	6914	24	100	55	NA	22	NA	18	39	43
INTER99	White	Denmark	6514	5	49	46	130	31	7	6	36	57
D.E.S.I.R.	White	France	3378	9	50	47	131	35	9	22	49	30
Rotterdam Study	White	Netherlands	3215	7	41	66	136	54	27	9	39	52
MDCS	White	Sweden	3199	17	40	56	139	53	14	6†	33†	61†
GLACIER	White	Sweden	2763	10	37	45	124	19	4	7	36	58
MESA	Mixed	USA	2424	10	47	61	132	35	28	20	49	30
FamHS	White	USA	2167	8	45	51	127	44	36	12	42	46
CHS	White	USA	1964	9	38	71	133	49	35	4	43	53
YFS	White	Finland	1370	0	43	38	120	9	7	15	47	38
DCH Study‡	White	Denmark	1297	0	45	56	135	47	13	5	32	63
DIOGENES‡ (controls)	White	Denmark	1002	0	51	54	135	38	7	6	36	58
DIOGENES‡ (weight gainers)	White	Denmark	813	0	49	53	135	42	10	5	35	60
PREDIMED-VALENCIA	White	Spain	940	2	36	67	147	84	63	38	46	16
BPRHS	Puerto Rican	USA	845	0	28	57	136	78	56	61	34	5
GOLDN	White	USA	818	0	50	49	118	26	21	10	40	50
Raine	Mixed§	Australia	728	2	48	20	117	4	0	15	39	46
InCHIANTI	White	Italy	647	0	45	64	142	64	49	2	30	68

See web appendix for full titles of studies.
SBP=systolic blood pressure.
*rs1446585 used as a proxy.
†rs309137 used as a proxy.
‡Subsamples from Danish Diet, Cancer and Health cohort.
§Dominantly white, white-admixed (participants with one or both white parents).

risk of hypertension. In addition we conducted a meta-analysis to summarize the results of eight randomized clinical trials assessing dairy intake intervention on changes in systolic blood pressure.

Methods

Study design and population

We used an instrumental variable approach to examine associations of dairy consumption with systolic blood pressure and risk of hypertension. We collected data from 22 observational studies with 171 213 participants within the CHARGE (Cohorts for Heart and Aging Research in Genomic Epidemiology) Consortium. All participants provided written informed consent. The web appendix describes the studies in the analysis.

To provide comprehensive evidence on associations of dairy intake with systolic blood pressure and risk of hypertension, we conducted a systematic review of previously published cohort studies and randomized clinical trials. In the web appendix, we describe the process of the systematic review in detail.

Dairy consumption

Dairy products included skim/low fat milk, whole milk, ice cream, yogurt, cottage/ricotta cheese, cream cheese, other cheese, and cream. In most of the studies, dairy intake was self reported by food frequency questionnaire. We calculated total dairy consumption as the sum of all dairy categories (see table 1 in the web appendix for a detailed description of dairy consumption in the included studies).

Outcome measures

The outcome of our Mendelian randomization included systolic blood pressure and risk of hypertension. Given that systolic blood pressure is superior to diastolic blood pressure as a major risk factor of cardiovascular disease, we used systolic blood pressure as the main outcome in our analysis (see table 1 in the web appendix for the detailed measurement of systolic blood pressure in the included studies). For participants taking antihypertensive drugs, we added 15 mm Hg to systolic blood pressure to adjust for treatment effects.[15-17] Hypertension was defined as a systolic blood pressure of 140 mm Hg or higher or current use of antihypertensive drugs.

SNP rs4988235

Table 1 in the web appendix shows genotyping platforms, genotype frequencies, Hardy-Weinberg equilibrium P values, and call rates for lactase persistence SNP rs4988235. The SNP rs4988235 was not genotyped or imputed in two studies; proxy SNPs (rs309137: r^2=0.77; rs1446585: r^2=1.00) were used instead.

Statistical analyses

We initially conducted statistical analyses within each included study in accordance with a standard analysis plan. As lactase persistence is inherited as a dominant trait,[3] we used dominant models (CC *v* CT/TT genotype) to examine associations of *LCT-13910* rs4988235 with dairy intake, systolic blood pressure, and risk of

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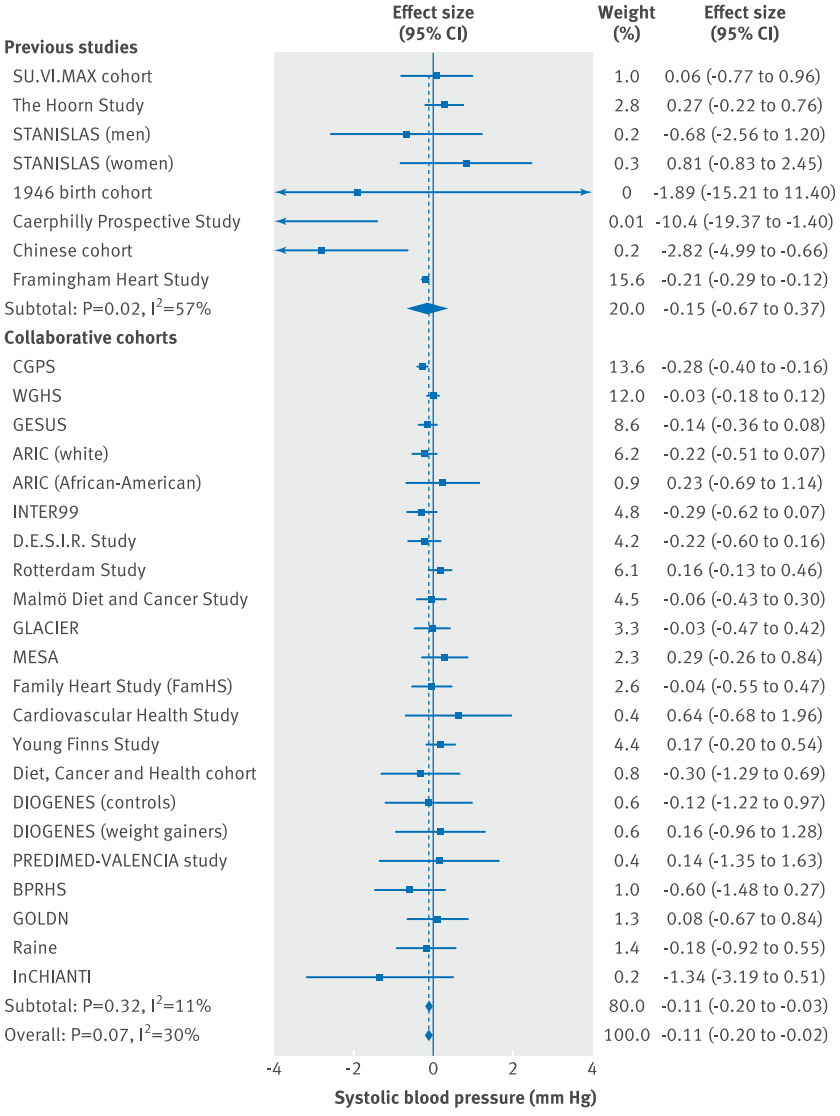

Fig 1 | Association of baseline dairy consumption (serving/day) with systolic blood pressure in observational cohort studies. Linear regression was used in collaborative cohorts adjusted for sex, ethnicity, region or country, and years of follow-up, as well as for age, body mass index, blood pressure/hypertension, smoking status, physical activity, total energy intake, and alcohol consumption at baseline

hypertension adjusting for baseline age, sex, ethnicity, and region. We examined associations of dairy consumption with systolic blood pressure and risk of hypertension using linear or logistic models adjusting for baseline age, body mass index, blood pressure, smoking status, physical activity, total energy intake, alcohol consumption, sex, ethnicity, region, and years of follow-up. For results collected from all studies using linear or logistic models, we combined results across studies using random effects models. We meta-analyzed the results of observed associations of dairy intake with systolic blood pressure and risk of hypertension within the CHARGE Consortium with results extracted from published cohort studies. The effect of dairy intake on systolic blood pressure from published randomized clinical trials was also meta-analyzed using a random effects model. Statistical heterogeneity across studies was assessed by Cochrane Q test, with P<0.1 indicating significant between study heterogeneity. In addition, we calculated the I^2 statistic to evaluate the percentage of heterogeneity that was due to between study variation.[18]

After pooling the association between *LCT-13910* rs4988235 and dairy intake across studies by meta-analysis, we quantified the strength of the single SNP as an instrumental variable by Z statistic and P value of the pooled effect estimate. We considered *LCT-13910* rs4988235 a strong instrumental variable if the Z statistic was more than 3.2 or the P value was less than 0.0016, which was equivalent to an F statistic greater than 10.[19 20] We used the instrumental variable ratio method to estimate the possible causal relation of dairy consumption with systolic blood pressure and risk of hypertension. The instrumental variable estimate was calculated as the ratio of the association of the instrumental variable with outcome to the association of the exposure with outcome. We estimated the variance of the instrumental variable ratio using first order Taylor expansion.[21]

We further conducted stratified analysis on the causal estimates of dairy intake with systolic blood pressure and risk of hypertension by frequency of CC alleles (≤12%, >12%), region or country (northern Europe, southern Europe, US), race (white, other), study design (cross sectional, prospective), and measurement of systolic blood pressure (self reported, clinical). We used metaregression to evaluate effect modification by each study level characteristics. In sensitivity analyses, we applied instrumental variable analysis within each study and combined the instrumental variable estimates through meta-analysis; we repeated our analyses using additive (we assumed 0, 1, and 2 for TT, CT, and CC alleles) and recessive models (CC/CT *v* TT). We conducted restriction analyses by excluding studies that used proxy SNPs, studies that used *LCT-13910* rs4988235 in Hardy-Weinberg disequilibrium, or studies where *LCT-13910* rs4988235 was not statistically significantly associated with higher dairy intake.

All meta-analyses were conducted at Harvard TH Chan School of Public Health using Stata version 11.2 (STATA Corp, College Station, TX).

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

Results

We included 22 studies with 171 213 participants from the CHARGE (Cohorts for Heart and Aging Research in Genomic Epidemiology) Consortium. Table 1 shows the baseline characteristics of the studies. Of the 22 studies, nine were conducted in the US, nine in countries in northern Europe, three in countries in southern Europe, and one in Australia. The frequency of CC alleles varied across studies. In most of the studies, participants were

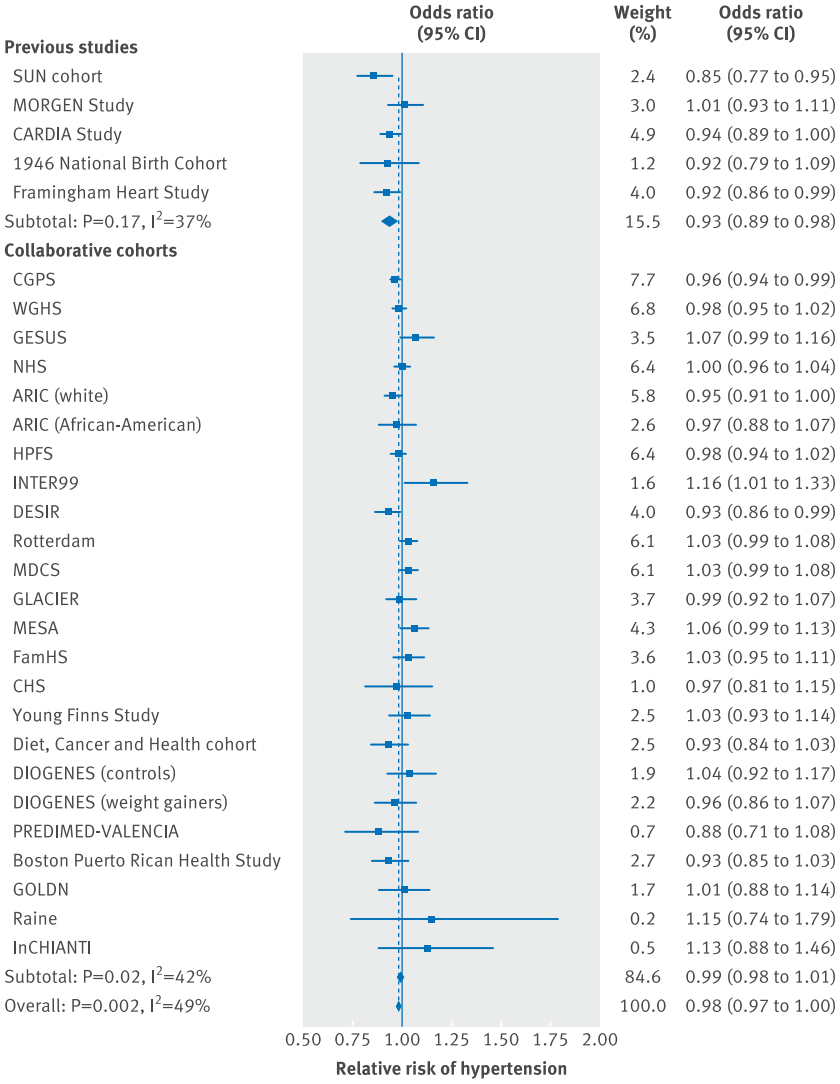

Fig 2 | Association of baseline dairy consumption (serving/day) with relative risk of hypertension in observational cohort studies. Logistic regression was used in collaborative cohorts adjusted for sex, ethnicity, region or country, and years of follow-up, as well as for age, body mass index, blood pressure/hypertension, smoking status, physical activity, total energy intake, and alcohol consumption at baseline

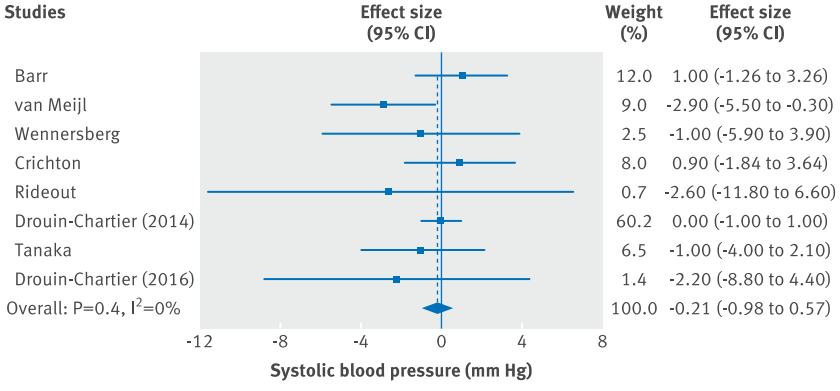

Fig 3 | Association of baseline dairy consumption (serving/day) with systolic blood pressure in randomized clinical trials

white, and dairy intake was assessed prospectively before measuring systolic blood pressure.

By conducting a systematic review, we additionally identified 10 published cohort studies with 26 119 participants and eight randomized clinical trials with 735 participants. Figure 1 in the web appendix shows the flowchart of study selection. The clinical trials examined the effect of dairy intake on systolic blood pressure over one month to 12 months of interventions.[22-29] In the cohort studies, seven assessed systolic blood pressure as the outcome[5-10 30 31] and five used hypertension as the outcome.[5 30-33] Tables 2 and 3 in the web appendix show the characteristics of the published trials and cohorts.

In observational analysis, each serving/day increase in dairy consumption was associated with lower systolic blood pressure (β=–0.11, 95% confidence interval –0.20 to –0.02 mm Hg; P=0.02) and was not associated with a lower relative risk of hypertension (odds ratio 0.98, 95% confidence interval 0.97 to 1.00; P=0.11) (figs 1 and 2). In the randomized clinical trials, however, dairy intake did not show a significant effect on changes in systolic blood pressure over one month to 12 months of interventions (comparing intervention with control group: β=–0.21, –0.98 to 0.57 mm Hg; P=0.60) (fig 3). No publication bias of included cohorts and clinical trials was found (systolic blood pressure in cohorts: Egger's test P=0.51; hypertension in cohorts: P=0.46; randomized clinical trials: P=0.33) (fig 2 in the web appendix).

Compared with the CC genotype, the CT/TT genotype of *LCT-13910* rs4988235 was associated with higher dairy consumption (0.23 (95% confidence interval 0.17 to 0.29) serving/day (about 55 g/day); P<0.001), and the Z statistic was 7.51, showing that the instrumental variable was strong and valid (fig 4). However, significant heterogeneity was found across studies (I^2=80.0%; P<0.001 for heterogeneity). Compared with the CC genotype, the CT/TT genotype of *LCT-13910* rs4988235 was not associated with systolic blood pressure (0.31, –0.05 to 0.68 mm Hg; P=0.09) or risk of hypertension (odds ratio 1.01, 95% confidence interval 0.97 to 1.05; P=0.27) (figs 5 and 6). Using *LCT-13910* rs4988235 as the instrumental variable, we estimated that genetically determined dairy consumption was not associated with systolic blood pressure (β=1.35, 95% confidence interval –0.28 to 2.97 mm Hg for each serving/day) or risk of hypertension (odds ratio 1.04, 0.88 to 1.24).

To explore sources of heterogeneity in the association of *LCT-13910* rs4988235 with dairy intake, we conducted stratified analyses by region or country, frequency of the CC genotype, race, study design, and measurement of systolic blood pressure. We classified Denmark, the Netherlands, Sweden, and Finland as northern European countries and Italy, Spain, and France as southern European countries. Among studies with a CC genotype frequency of 12% or less, or studies conducted in northern European countries, we found no heterogeneity of *LCT-13910* rs4988235 with dairy intake, and the instrumental variable remained strong in both subgroups. Genetically determined dairy consumption was unrelated to systolic blood pressure and risk of hypertension within each stratum, which was consistent with the main finding

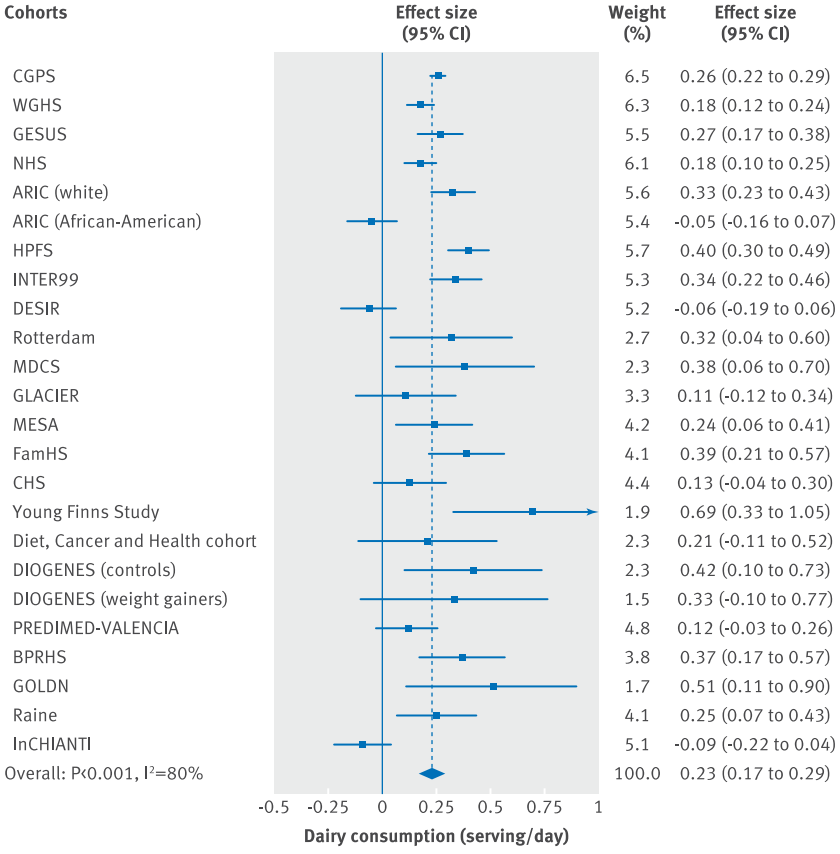

Fig 4 | Association of SNP rs4988235 with dairy consumption using dominant model (CT/TT *v* CC genotype). Linear regression adjusted for baseline age, sex, ethnicity, and region or country

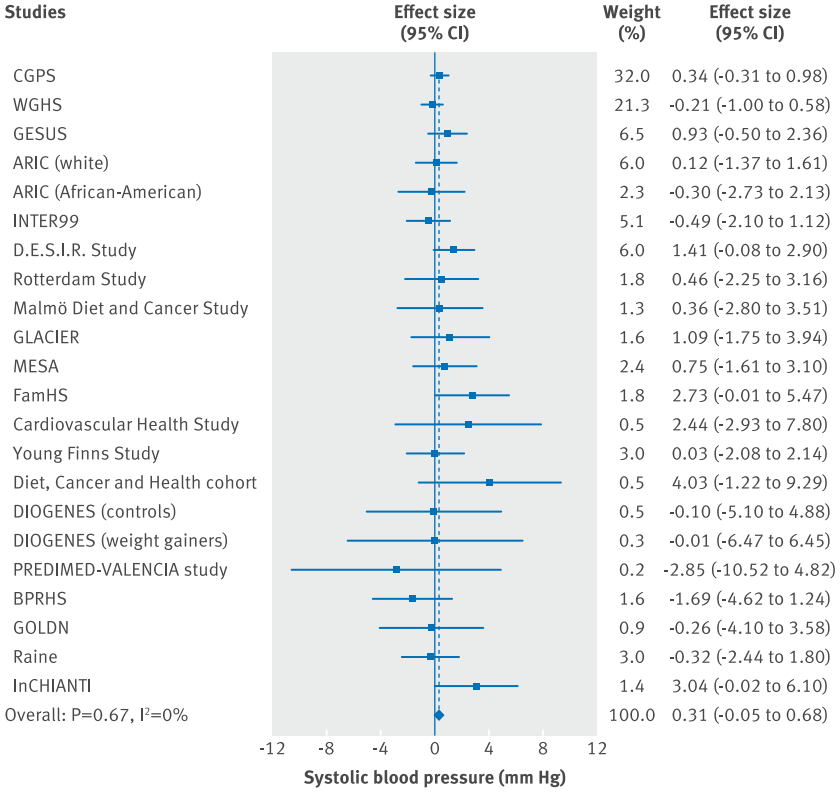

Fig 5 | Association of SNP rs4988235 with systolic blood pressure using dominant model (CT/TT *v* CC genotype). Linear regression adjusted for baseline age, sex, ethnicity, and region or country

(table 2). No effect modification on causal estimates was found by CC frequency, region or country, race, study design, and systolic blood pressure measurement.

In sensitivity analyses, we applied the instrumental variable analysis within each study and combined the instrumental variable estimates using meta-analysis. The results were consistent with the main findings (fig 3 in the web appendix). We examined the associations of dairy consumption with systolic blood pressure and risk of hypertension by modeling the *LCT-13910* genotype in recessive and additive inheritance manner (figs 4 and 5 in the web appendix). Genetically determined dairy consumption was not associated with systolic blood pressure or risk of hypertension using the recessive model, and it was weakly associated with higher systolic blood pressure using the additive model (table 4 in the web appendix).

In restriction analysis, the instrumental variable estimates were consistent with the main findings when excluding studies that used proxy SNPs, studies that used *LCT-13910* rs4988235 in Hardy-Weinberg disequilibrium, or studies where *LCT-13910* rs4988235 was not statistically significantly associated with higher dairy intake using dominant models.

Discussion

In this study, using Mendelian randomization analysis in 32 studies (22 observational studies, 10 previously published cohort studies) with 197 332 participants, we examined the potential causal effect of dairy consumption on systolic blood pressure and risk of hypertension. Using the *LCT-13910* gene variant affecting lactase persistence as the instrumental variable, our study showed that genetically determined dairy intake did not affect systolic blood pressure or risk of hypertension. Furthermore, a meta-analysis of the results from published randomized clinical trials showed that dairy consumption had no effect on changes of systolic blood pressure in response to interventions over one month to 12 months.

Strengths and weaknesses of this study

Our study has several strengths. First, we carried out a large instrumental variable analysis on the causality of dairy intake on systolic blood pressure and hypertension. The large sample size provided us with enough power to estimate the causal effect of dairy intake on systolic blood pressure. Second, the single nucleotide polymorphism (SNP) rs4988235 for lactase persistence is a well established variant associated with dairy intake, with a solid biological basis, and is therefore a highly valid instrumental variable. Third, we summarized published randomized clinical trials on dairy consumption with systolic blood pressure. Although clinical trials have shorter follow-up time than cohort studies, they still provided further supportive evidence to the instrumental variable results.

Our study has several limitations. First, given the variability of the CC allele across studies and the different prevalence of hypertension across countries, population stratification might exist. However, as most of the studies included were genetically homogeneous, we performed instrumental variable analysis within each study first and

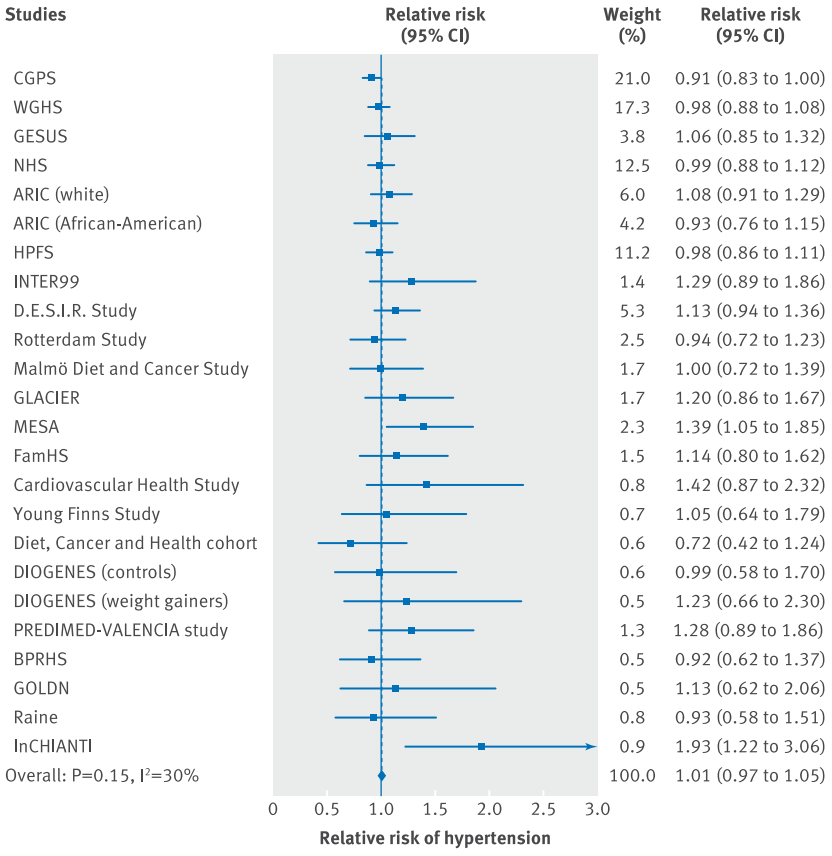

Fig 6 | Association of SNP rs4988235 with relative risk of hypertension using dominant model (CT/TT *v* CC genotype). Logistic regression adjusted for baseline age, sex, ethnicity, and region or country

combined the instrumental variable results through meta-analysis. The instrumental variable results were consistent with the main findings. Second, the pleiotropic effect of SNP rs4988235 is not known. However, SNP rs4988235 was located in the MCM6 gene upstream from *LCT-13910*, and neither gene has been found to have additional biological function besides lactase persistence.[13] Third, dairy consumption was self reported by questionnaire and might be affected by measurement errors. If measurement errors were random, the observed associations would be biased to the null. However, the results for instrumental variable estimates would not be biased, although the confidence interval might be larger. Fourth, we included total dairy intake as the main exposure; however, lactase content differs between dairy products. For example, Swiss cheese and mozzarella contain trivial amounts of lactase. Similar to the measurement error of dairy intake, the variability in lactase content of dairy products might not bias the instrumental variable estimates but might widen the confidence intervals. Fifth, several studies examined dairy consumption and systolic blood pressure using a cross sectional study design, and even if instrumental variable analysis was used this might result in reverse causation. However, no statistically significant effect modification by study design was found in stratified analysis, indicating that reverse causation caused by study design might be minimal.

Strengths and weaknesses in relation to other studies

In our study we observed an inverse association between dairy intake and systolic blood pressure. Consistently, cross sectional studies showed an inverse association between dairy intake and systolic blood pressure.[34-36] Previous cohort studies have been summarized in two meta-analyses.[11 12] One meta-analysis involving approximately 45 000 participants showed that dairy products were associated with lower risks of raised systolic blood pressure.[11] In line with this, another meta-analysis, which included nine cohort studies with a sample size of 57 256, found an inverse association between dairy foods and risk of hypertension.[12] However, in both meta-analyses, the associations of high fat dairy products, including whole milk, cream, and cream cheese, and low fat dairy products, including skim milk and yogurt with systolic blood pressure were inconsistent. In the two published meta-analyses, the observed inverse association was mainly due to consumption of low fat dairy products.[11 12] Furthermore, a meta-analysis summarizing 14 clinical trials found that probiotic fermented milk, including yogurt, resulted in a statistically significant reduction in systolic blood pressure.[37] Clinical trials also showed that tripeptides and peptides derived from milk have hypotensive effects in prehypertensive and hypertensive participants.[38 39]

Possible explanations and implications

Compared with the CC genotype, the CT/TT genotype was associated with 0.23 serving/day (about 55 g/day) higher dairy intake. In previous cohort studies, a 55 g/day increment in dairy intake was estimated to be statistically significantly associated with 0.03 mm Hg lower systolic blood pressure, and 1%, 2%, and 1% lower risks of hypertension,[12] type 2 diabetes,[40] and cardiovascular disease,[41] respectively. However, in our study, the CT/TT genotype was associated with a 0.31 mm Hg higher systolic blood pressure, and genetically determined dairy consumption did not decrease systolic blood pressure or risk of hypertension using instrumental variable estimation. Moreover, the meta-analyzed results of clinical trials showed that dairy intake had no effect on changes in systolic blood pressure. There could be two reasons that the reported associations from observational studies were inconsistent with our instrumental variable results. First, even if yogurt and specific nutrients in dairy such as milk peptides have antihypertensive effects, specific dairy products such as yogurt only compose a small fraction of total dairy products and could not explain the general observational association between dairy intake and outcome. Second, higher low fat dairy intake was more likely to be associated with a healthy diet and lifestyle.[42] Therefore, the observed inverse association of particularly low fat dairy intake with systolic blood pressure might be due to confounding of intake of other food items and a healthy lifestyle. However, as one fundamental assumption for the instrumental variable to be valid is that the instrumental variable is associated with the outcome only through the exposure under study,[43]

Table 2 | Stratified analysis on causal estimates of dairy consumption (serving/day) with systolic blood pressure (mm Hg) and risk of hypertension (odds ratio). Values in brackets are 95% confidence intervals unless stated otherwise

Variables	No of observations	Instrumental variable			SBP		Hypertension	
		SNP rs4988235 with dairy intake	Z statistic (P value)	I^2 (%) (P value)	SNP rs4988235 with SBP	Dairy intake with SBP, instrumental variable estimation	SNP rs4988235 with risk of hypertension	Dairy intake with risk of hypertension, instrumental variable estimation
CC genotype frequency*:								
≤12%	14	0.27 (0.22 to 0.31)	11.64 (<0.001)	34.4 (0.10)	0.27 (−0.14 to 0.67)	1.00 (−0.51 to 2.51)	0.99 (0.93 to 1.04)	0.96 (0.78 to 1.19)
>12%	9	0.21 (0.08 to 0.34)	3.26 (0.001)	87.4 (<0.001)	0.30 (−0.55 to 1.15)	1.43 (−2.71 to 5.57)	1.03 (0.95 to 1.11)	1.15 (0.79 to 1.68)
Region or country†:								
Northern Europe	10	0.28 (0.23 to 0.33)	11.11 (<0.001)	10.5 (0.31)	0.37 (−0.13 to 0.87)	1.32 (−0.48 to 3.12)	0.96 (0.89 to 1.03)	0.86 (0.67 to 1.12)
Southern Europe	3	−0.01 (−0.14 to 0.11)	0.22 (0.83)	5.2 (0.08)	NA	NA	NA	NA
USA	10	0.25 (0.16 to 0.34)	5.32 (<0.001)	51.5 (<0.001)	0.01 (−0.59 to 0.62)	0.04 (−2.38 to 2.46)	1.01 (0.96 to 1.07)	1.04 (0.84 to 1.29)
Race:								
White	20	0.23 (0.17 to 0.30)	7.22 (<0.001)	78.8 (<0.001)	0.31 (−0.09 to 0.70)	1.35 (−0.41 to 3.11)	1.03 (0.97 to 1.09)	1.14 (0.88 to 1.47)
Other	4	0.20 (0.01 to 0.39)	2.05 (0.04)	86.4 (<0.001)	0.36 (−0.67 to 1.38)	1.80 (−3.60 to 7.20)	1.06 (0.89 to 1.27)	1.34 (0.53 to 3.40)
Study design:								
Cross sectional	9	0.28 (0.16 to 0.40)	4.51 (<0.001)	73.7 (<0.001)	0.36 (−0.01 to 0.73)	1.29 (−0.15 to 2.72)	1.03 (0.88 to 1.20)	0.96 (0.75 to 1.24)
Cohort	15	0.21 (0.13 to 0.29)	5.41 (<0.001)	36.8 (<0.001)	0.09 (−0.14 to 0.32)	0.43 (−0.68 to 1.54)	1.03 (0.98 to 1.09)	1.10 (0.95 to 1.27)
SBP measurement:								
Self reported	5	0.25 (0.15 to 0.34)	5.23 (<0.001)	17.0 (0.002)	−0.14 (−0.84 to 0.57)	−0.56 (−3.39 to 2.27)	1.01 (0.93 to 1.09)	1.04 (0.85 to 1.27)
Clinical	19	0.23 (0.15 to 0.31)	5.60 (<0.001)	97.8 (<0.001)	0.48 (0.05 to 0.90)	2.09 (0.10 to 4.07)	1.05 (0.98 to 1.14)	1.04 (0.90 to 1.21)

SNP=single nucleotide polymorphism; SBP=systolic blood pressure; NA=not available.
*InCHIANTI was excluded owing to an extremely low CC frequency of 2%.
†Raine study was not included as it was conducted in Australia.

we could not separate the effect of individual dairy products in our study to further explain the inconsistency between observational and instrumental results using the current instrumental variable. And it is difficult to find a specific instrumental variable for each dairy product.

To tackle the heterogeneity of the association between SNP rs4988235 and dairy intake across studies, we conducted stratified analysis by CC frequency and region or country. SNP rs4988235 was consistently associated with higher dairy intake across subgroups, showing the robustness of our instrumental variable. No heterogeneity was found among studies conducted in northern Europe or among studies with a CC frequency of 12% or less, perhaps because these populations consume a relatively high amount of dairy products,[44] and SNP rs4988235 was found to be associated completely with lactase persistence in north Europeans.[13] No associations of genetically determined dairy intake with systolic blood pressure and risk of hypertension were found in both subgroups, which were consistent with our main finding.

Conclusion

The weak inverse association between dairy intake and systolic blood pressure in observational studies was not supported by our comprehensive instrumental variable analysis and systematic review of existing clinical trials.

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Supplementary appendix: additional information